The Effect of Corticosteroids on Urinary Calcium Excretion. A Pilot Study

Kortikosteroidlerin İdrar Kalsiyum Atılımına Etkileri. Pilot Çalışma

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Özet

Amaç: Kortikosteroidler, nefrotik sendrom ve bronşiyal hiperreaktivite tedavisindeki temel ilaçlar olup, yüksek dozda ve uzun süre kullanılmaları gerekebilir. Sistemik kortikosteroidlerin hiperkalsiüriye neden olduğu, klinik ve deneysel çalışmalarda gösterilmiştir. Bu çalışmada, nefrotik sendrom ve bronşiyal hiperreaktivite tanılı çocuklarda, kortikosteroidlerin idrar kalsiyum atılımı üzerindeki etkisini ve ilişkili parametreleri araştırmayı amaçladık. Gereç ve Yöntem: Nefrotik sendrom ve bronşiyal hiperreaktivite tanılı, 1-15 yaş arası 39 çocuk ile aynı yaş ve cinsiyetteki 15 sağlıklı kontrol grubu çocuk çalışmaya dahil edildi. Nefrotik sendrom tanılı 2 mg/kg/g oral prednizolon alan 19 hasta grup 1 olarak ve inhale 2x200 µgr budesonid tedavisi alan bronşiyal hiperreaktivite tanılı 20 hasta grup 2 olarak çalışmaya alındı. Tüm çocukların kemik yapım (serum osteokalsin ve alkalen fosfataz), kemik yıkım (idrar deoksipiridinolin/kreatinin) ve kemik metabolizma belirteçleri (paratiroid hormon, kalsiyum ve fosfat) çalışıldı. Bulgular: Nefrotik sendrom grubunda, tedavi sonrası idrar kalsiyum/kreatinin oranında artış saptandı. Serum osteokalsin seviyesi, oral prednizolon tedavisi alan nefrotik sendrom grubunda azalmış saptandı. Fakat idrar deoksipridinolin crosslink/kreatinin oranı, beklenenin aksine, hem nefrotik sendrom hem de bronşiyal hiperreaktivite tanılı hastalarda düşük saptandı. Tartışma: Bu çalışmada, oral prednizolon tedavisi kullanımının renal kalsiyum atılımını arttırdığını fakat inhale budesonid kullanımının arttırmadığını gördük. Oral prednizolon tedavisinin kemik yapımını baskıladığını düşünüyoruz. Düşük bulunan idrar deoksipridinolin crosslink/kreatinin oranıyla ilgili, vaka sayısı çok olan daha fazla prospektif çalışma gereklidir.

Anahtar Kelimeler

Bronşiyal Hiperreaktivite; Kalsiyum; Kortikosteroid; Nefrotik Sendrom

Abstract

Aim: Corticosteroids are the main drugs in the treatment of nephrotic syndrome and bronchial hyperreactivity and can be used for long periods in high doses. From clinical use and experiments, systemic corticosteroids are known to cause hypercalciuria. In this study we aim to determine the effect of corticosteroids on urinary calcium excretion and to assess related parameters in children with chronic disease. Material and Method: Thirty-nine children with nephrotic syndrome and bronchial hyperreactivity from ages 1-15 and 15 same-aged healthy controls of the same sex are included in the study. Nineteen patients with nephrotic syndrome using 2 mg/kg/day oral prednisolone are included in group 1, and 20 patients with bronchial hyperreactivity who use inhaled 2x200 µgr budesonide are included in group 2. All children's bone formation (serum osteocalcin and alkaline phosphatase), resorption (urine deoxypyridinoline crosslinks/creatinine), and metabolism markers (parathyroid hormone, calcium, and phosphate) were analyzed. Results: Post-treatment urinary calcium/creatinine ratio was increased in the nephrotic syndrome group. Osteocalcine levels were found decreased in nephrotic syndrome patients who take oral prednisolone treatment. Urine deoxypyridinoline crosslinks/creatinine ratio levels were found low in both nephrotic syndrome and bronchial hyperreactivity patients, contrary to expectations. Discussion: In this study we found that oral prednisolone usage increased renal calcium excretion while inhaled budesonide did not increase renal calcium excretion. We believe that oral prednisolone repressed the bone formation. To further investigate low urine deoxypyridinoline crosslinks/creatinine ratio, more prospective studies with a greater number of participants are required.

Keywords

Bronchial Hyperreactivity; Calcium; Corticosteroid; Nephrotic Syndrome

DOI: 10.4328/JCAM.4457 Received: 02.03.2016 Accepted: 22.03.2016 Printed: 01.07.2016 J Clin Anal Med 2016;7(4): 524-8
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Introduction

Corticosteroids are one of the main drugs commonly used in the treatment of chronic diseases to alleviate anti-inflammatory, antiallergic, and immunosuppressive effects of the diseases [1]. In children, nephrotic syndrome (NS) and bronchial hyperreactivity (BH) are the diseases for which steroids are the first choice treatment [2]. Corticosteroids show important side effects that influence many systems, with several hypotheses proposed regarding one of the rare effects, viz., hypercalciuria (HC) [3]. Only a limited number of studies on the hypercalciuric effect of corticosteroids use (Cs) in children were available in the literature.

Turkey is a country where pediatric urinary tract stone disease is endemically prevalent [4]. The global incidence of HC in children was reported to be 0.6-12.7%; 2.8-12.5% occur in Turkey and 9.6% in Aydın city [5-7]. HC can cause hematuria, recurrent urinary tract infections, abdominal pain, and urinary incontinence [5-6]. Therefore, the diagnosis and treatment of HC is crucial, especially to explain the causes and to avoid unnecessary and detailed tests.

Systemic Cs were reported to cause HC by inhibiting the osteoblastic activity and increasing the osteoclastic activity in the bone, as well as by increasing urinary calcium (Ca) excretion from the kidney, according to some studies [7]. Serum alkaline phosphatase (ALP) and osteocalcin levels show osteoblastic activity in the bone. To clarify the aspect of bone osteoclastic activity, the urinary deoxypyridinoline/creatinin ratio can be used. Deoxypyridinoline plays a role in the fixation and strengthening of type I collagen in the bone and its excretion via urine in the case of collagen destruction [3].

In this study we aim to evaluate the role of the Cs, used both in the oral and inhalation forms, on the urinary excretion of Ca and the factors affecting it.

Material and Method

Thirty-nine children with NS and BH from 1 to 15 years of age, and 15 healthy controls of the same ages and sex were included in the study. Written informed consent was received from the parents prior to treatment, and the study protocol was approved by the local ethics committee of Adnan Menderes University. Patients who had used oral, parenteral, or inhaled Cs, Ca, and vitamin D within three months of the study, and those with chronic diseases (such as cystic fibrosis, chronic pulmonary disease, and bronchiolitis obliterans) were excluded from the study. Patients and their first-degree relatives were investigated for asthma, eczema, allergic rhinitis, recurrent wheezing, urticaria, and nephrolithiasis. Only patients experiencing their first attack were included in the study. The non-control patients were divided into two groups. Group 1 included 19 patients taking Cs to treat NS, by 2 mg/kg/day oral prednisolone treatment for one month. Group 2 included 20 patients taking Cs to treat BH, using inhaled 2x200 µgr budesonide for three months.

The NS cases were followed up in the clinic and categorized as those with onset or in remission. Patients with edema, severe proteinuria (three consecutive days of >40 mg/m2/hour or protein/creatinine >2g/g and +3-4 protein on the urine strip), and hypoalbuminemia <2.5 g/dl) were defined as having an "onset." Those who had experienced three days of protein release in the urine < 4 mg/m2/hour and 0 or trace amount of protein or protein/creatinine < 0.2 g/g on the urine strip were defined as being in remission [2].

According to the criteria for the global initiative for asthma (GINA), one of the indicators in the clinic, the BH cases were defined as having moderate persistent asthma (using the B2 agonist every day, having daily asthma symptoms, and experiencing more than three symptomatic nights in a week). Asthmatic exacerbations are termed episodes characterized by a progressive increase in the symptoms of shortness of breath, cough, wheezing, or chest tightness and progressive decrease in lung function [8].

Blood and urine samples of the patients in the NS and BH groups were collected at the beginning of the attack and at remission (four weeks post treatment) and stored at -80oC. Urine deoxypyridinoline crosslinks/creatinine (uDPC/Cr) were considered bone resorption markers, whereas the sOsteocalcin and ALP values were defined as bone formation markers, and PTH, Ca, and P were considered bone metabolism markers. Serum calcium (sCa), phosphate, sodium, potassium, creatinine, and ALP were analyzed using the standard methods. Because the children in the nephrotic syndrome group had serum albumin values of 2.5 mg/dl, corrected Ca was used. Intact PTH and osteocalcin tests were measured with the hormone analyzer. Urinary prostaglandin E2 (uPGE2) measurement was performed with the ELISA method. The urinary N-acetyl-B-D glucosaminidase (uNAG) level was studied employing the spectrophotometric method using the Diazyme N-acetyl-B-D glucosaminidase commercial kit (catalog no: DZ062 A). The urine deoxypyridinoline crosslinks (DPC) test was measured utilizing the competitive enzyme immunoassay method.

The Ca (mg/dl), Creatinine (Cr) (mg/dl) ratio (uCa/Cr) was measured in the morning fasting urine to obtain the calcium excretion. In our study, the HC limits were defined as above the 0.21 value of the uCa/Cr ratio, according to the HC study done earlier in Aydın involving 2500 children [9]. Because diet is one of the main factors affecting calcium excretion, dietary calcium intake accounted for all of the cases in the three days prior to sampling. Normal glomerular filtration rate (>90 ml/min/1,73 m2) was estimated using the Schwartz Formula [10].

Compliance with the normal distribution of quantitative variables was analyzed with the Kolmogorov-Smirnov test. Paired t-test or one-way ANOVA was used to compare data in accordance with the normal distribution between the groups. Descriptive statistics were shown as average standard deviation. Wilcoxon signed rank test for paired data was used. Kruskal-Wallis test was used for between-group comparisons of data not suitable for normal distribution. Descriptive statistics are shown as median (25-75 percentile); $p < 0.05$ was considered as statistically significant.

Results

The clinical and demographic data of the study groups are listed in Table 1. Fifty-four patients were included in the study; 19 cases form the NS group, 20 cases in the BH group, and 15 cases in the control group. In the nephrotic syndrome group, 84.2% of the cases had minimal lesion disease (MLD), 10.5% showed membranoproliferative glomerulonephritis (MPGN), and 5.3%

Table 1. Clinical and demographic data of the study groups

	Group NS (n=19)	Group BH (n=20)	Group Control (n=15)
Age(year)	7.07±3.07	7.92±3.01	8,7±3.49
Body weight (kg)	25±1.4	26.3±1.7	27.4±0.8
Height (cm)	120±10	115±12	127±14
Sex			
female (%)	36.8	50	46.7
male (%)	63.2	50	53.3
Blood pressure (mmHg)	120/80	95/63	90/60
Daily dietary calcium intake (mg/day)	577.6± 286.6	435.5±178.5	496.2±226.2
Stone disease in the family (%)	15.8	50	0
Family history of atopy (%)	5.3	85	0

suffered from Henoch-Schönlein purpura (HSP). In the bronchial hyperreactivity group, 80% of the cases had asthma while 20% of the cases showed asthma+gastroesophageal reflux. No differences were observed in terms of sex, body weight, height, and dietary Ca intake among the groups (p>0.05). Although a family history of stone disease was identified more in group BH than in the others, it showed no statistical significance (p=0.064). Family history of atopy was significantly higher in the BH group than in the NS group (p<0.001). Also, higher blood pressure prior to treatment was recorded in the NS group than in the other groups (p< 0.05).

In the assessment of the pre-treatment values among the groups, the urinary Ca/Cr ratio was significantly lower in the NS group than in the BH group (p=0.025) (Fig. 1). The urinary NAG/Cr ratio was higher in the NS group than in the BH and control groups (p<0.001) and the urinary PGE2/Cr ratio was higher in the NS group than in the control (p=0.038) (Table 2). In the control group, a positive correlation was found between sOsteocalcin, ALP (p=0.006, r=0.673), and NAG/Cr (p=0.019, r=0.595) and between PGE2/Cr and DPC/Cr (p=0.001, r=0.746).

In the post-treatment assessment, the sOsteocalcin values were found to be significantly lower in the NS group than the control (p=0.027) (Fig.2) and the ALP values were found to be significantly lower in the NS than in the other two groups (p=0.001). No difference was observed in the post-treatment sCa levels among the groups (p=0.132). The urinary DPC/Cr ratio was found to be lower in the NS and BH groups than in the control (p=0.001) (Fig. 3). No difference was observed in any of the other serum and urine tests among the groups (p>0.05) (Table 2). The post-treatment uCa/Cr and DPC/Cr values were found to be significantly correlated (p=0.001, r=0.706) in the nephrotic syndrome group.

In the nephrotic syndrome group, the post-treatment uCa/Cr ratio was found to be higher than the pre-treatment values of uCa/Cr (p= 0.002) (Fig. 1). The post-treatment serum ALP and urinary DPC/Cr levels were found to be lower than those of the pre-treatment (p=0.002, p<0.001, respectively). The serum osteocalcin levels were insignificantly lower post treatment. No difference was recorded between the pre- and post-treatment results for the other values (p>0.05) (Table 2).

In the bronchial hyperreactivity group, the post-treatment uDPC/Cr ratio was found to be lower than the pre-treatment uDPC/Cr ratio (p=0.001) (Fig. 3). The pre- and post-treatment values of osteocalcin and the other parameters were not found to show significant difference (p>0.05).

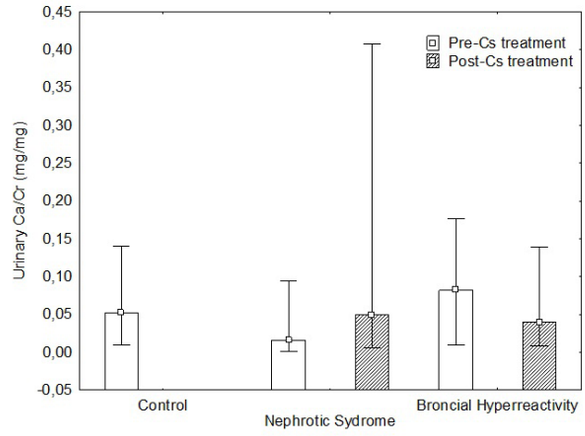

Figure 1. Pre-Cs and post-Cs treatment uCa/Cr values of groups. (Descriptive statistics was used median and non-outlier range)

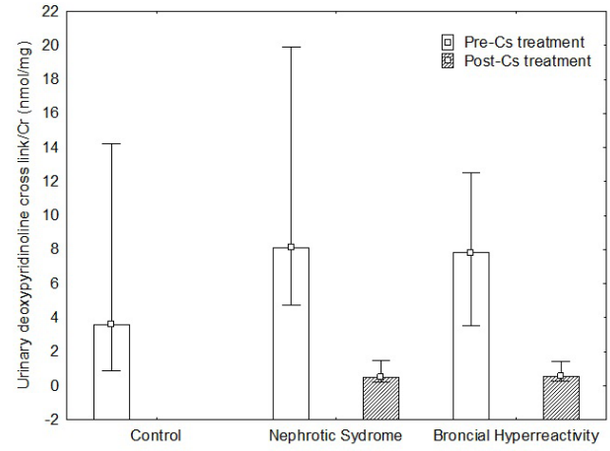

Figure 2. Pre and posttreatment sOsteocalcine values of groups. (Descriptive statistics was used median and non-outlier range)

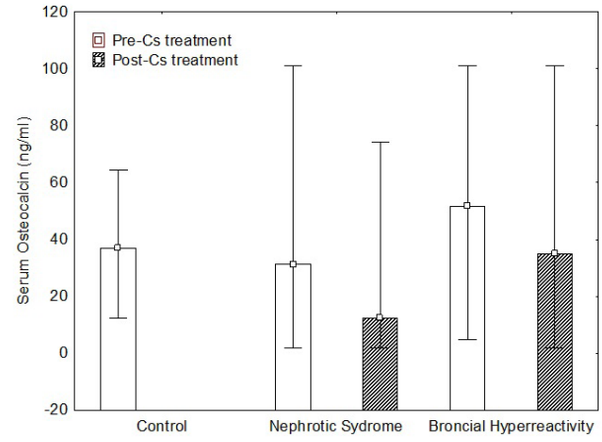

Figure3. Pre and posttreatment uDPC/Cr values of groups. (Descriptive statistics was used median and non-outlier range)

Table 2. Comparison of pre-Cs and post-Cs treatment values of groups NS and BH

	Group NS (n=19)			Group BH (n=20)			Group Control (n=15)
	Pre-Cs	Post-Cs	p* value	Pre-Cs	Post-Cs	p** value	
Bone metabolism markers							
PTH (pg/ml)	68.9±45.7	51.6±26.5	NS	45.8±15.2	50.0±23.5	NS	61.8±31.6
Ca	9±0.7	9±0.4	NS	9.3±0.5	9.3±0.7	NS	9.3±0.3
P	5.2±0.8	4.9±1.7	NS	4.9±0.7	4.6±0.5	NS	4.7±0.7
Bone formation markers ALP (IU/L)	177.1±70.5	127.2±50.2	0.002	233.1±179	184±64.6	NS	202.6±52.6
uNAG/Cr (IU/mg) median	0.08	0.04	NS	0.02	0.02	NS	0.03
(25-75percentile)	(0.06-0.13)	(0.02-0.08)		(0.01-0.04)	(0.01-0.05)		(0.01-0.06)
uPGE2/Cr (pg/mg) median	3.9	3.9	NS	2.9	3.2	NS	3.1
(25-75percentile)	(3.4-7.2)	(3-6.7)		(2.4-4.2)	(2.8-4)		(2.4-4.7)

BH: Bronchial hyperreactivity, NS: Nephrotic syndrome, Ca: Calcium, Cs:Corticosteroid, P: Phosphorus, uNAG/Cr: urinary N- acetyl glucosamine/creatinine, uPGE2/Cr: urinary prostaglandin/creatinine, sALP: serum alkaline phosphatase, sPTH:serum parathyroid hormone, p*value:Comparison of pre and post CS in nephrotic syndrome group, p** value:Comparison of pre and post CS in bronchial hyperreactivity group, NS: Non significiant

Discussion

In this study, we found that the usage of oral prednisolone increased renal Ca excretion, whereas the usage of inhaled budesonide caused no adverse effect. In the NS group, the osteocalcin levels as an indicator of bone formation were found to decrease. Also, the uDPD/Cr level, as an indicator of bone resorption, was lower in both the NS and BH patients, contrary to expectation.

Osteocalcin is a specific indicator for osteoblastic activity [7]. In some studies a drop in the sOsteocalcin levels with high-dose inhaled corticosteroid usage was reported [7,11], whereas in some other studies, no such difference was reported in sOsteocalcin levels with budesonide usage [12]. In children diagnosed with congenital adrenal hyperplasia and on oral steroid treatment for more than two years, the bone mineral density was found to be normal, the sOsteocalcin level was found to be low, while the uDPD/Cr level was high [13]. Inhaled budesonide was reported to exert low systemic effects and bioavailability. In our study, the sOsteocalcin levels, one of the bone formation markers, was found to have decreased in the NS patients, although it showed no change in the BH patients using 400µgr inhaled budesonide for three months. In conclusion, the type, dosage, and period of usage were believed to be effective in maintaining the sOsteocalcin level.

According to Wetzson RJ et al. [14], bone specific ALP was found to be low in children with steroid sensitive-NS compared with the control group. According to Aceto [15] and Bak et al. [16], no differences were observed during the different stages of treatment for calcium, phosphate, alkaline phosphatase, and 25-OH vitamin D. Vitamin D-binding globulin and 25-hdroxy D3 were low in the nephrotic urine [16]. Serum Ca and the most active vitamin D metabolites, 1.25-dyhidroxy D3 were normal or low, and serum parathyroid hormone was normal or high in those with nephrotic syndrome [16]. However, the serum vitamin D levels could not be assessed in this study. Therefore, we are unable to comment on vitamin D. In our study, no differences were obtained in any of the bone metabolism markers: Ca, P, and PTH. In the NS group the ALP level dropped significantly after treatment. These results show a decrease in the osteoblastic activity in the bone with the use of oral Cs. In the BH group, we found no difference at all with this dosage and periods of use of inhaled Cs. This demonstrated that inhaled Cs did not exert systemic effects.

Measurements of the type I collagen metabolites (the predominant collagen in bone) such as DPC have been reported to be useful for monitoring the bone turnover in many different disorders and drug usages [17]. The urine deoxypyridinoline level, which is a bone turnover marker, is expected to increase with the use of Cs. To our knowledge, a few studies are available on the effect of Cs therapy on the urine deoxypyridinoline crosslink level, and Rao et al. [18] reported an increase in the post-treatment uDPC/Cr levels in children on a 20-month inhaled budesonide or fluticasone therapy. But Ton et al. [11] also recorded a decrease in the post-treatment uDPC/Cr level in children on Cs. They associated this with the adaptation of the bone to the prednisolone treatment. Koşan et al. [19] demonstrated an increase in the urinary DPC/Cr excretion at the 4th and 12th weeks of treatment in children with nephrotic syndrome. However, in our study, different post Cs treatment levels of DPC/Cr were found in the NS and BH patients, which were low compared with the values of the pretreatment levels and control group levels. The findings of the present study revealed that the etiology was unknown for the lower post-treatment DPD/Cr levels in the NS and BH participants compared with the pre-treatment DPD/Cr levels and those of the control.

Many articles stated that the inhaled Cs neither influenced nor decreased the excretion of urinary Ca in children [8, 20-21]. Bootsma et al. [20] reported that a nine-week treatment of 750 µg/day fluticasone and 1500 µg/day beclomethasone showed no effect on the spot urinary Ca excretion. Akil et al. [8] also reported lower spot uCa/Cr levels in children diagnosed with asthma taking approximately 400-600 µg/day inhaled budesonide as treatment for a year, compared with the healthy children. However, in the study by Bentur et al., [22] in 16% of children taking 400 µg/gün inhaled budesonide for two months, the post treatment uCa/Cr level was found to significantly increase.

Not many publications related to the hypercalciuric effects of oral Cs in children with nephrotic syndrome are available. Düzen et al. [23] reported an increase in the levels of urinary calcium excretion in patients on 10 mg/day prednisolone treat-

ment for one month. Similarly, Koşan et al. [19] reported an increase in the levels of urinary calcium excretion during the 4th and 12th weeks of steroid treatment in children with NS. Our results showed that in the NS group, the uCa/Cr ratio which had increased post treatment was found to be highly positively correlated to the post-treatment DPC/Cr. We also observed a decrease in the osteocalcin levels post steroid treatment. From these findings, we concluded that a one-month usage of oral corticosteroids resulted in an increase in the bone resorption, as well as a decrease in bone formation by way of systemic effects. However, the BH group revealed no change in the levels of urinary Ca excretion even after utilizing 400 mcg of inhaled budesonide for two months.

The NAG/Cr ratio was seen to increase in idiopathic HC due to the primary tubular disorder [24]. The increased NAG/Cr ratio that had been recorded as high, prior to the treatment in the NS group, is believed to be related to the tubular inflammation due to the disease itself. Also, the post-treatment NAG/Cr levels were not found to significantly differ from the values prior to treatment in both the NS and BH groups. These results demonstrated that oral and inhaled Cs usage has no effect on the proximal tubules.

Prostaglandin E2 is well recognized for its role in HK by increasing the 1.25(OH)2 D synthesis [25]. In our study the uPGE2/Cr levels were found to be higher in the NS group than in the control group (p=0.038). Also, in the NS and BH post-treatment values, the uPGE2/Cr, which is highly and positively correlated with the DPC/Cr, was assumed to affect the bone resorption.

This study has limitations because the number of cases studied was small and vitamin D levels could not be investigated.

Conclusion

The short-term usage of moderate and low-dose inhaled steroids was found to have no effect on the osteoblastic and osteoclastic activities or on renal Ca excretion. However, it was observed that one-month of oral steroid usage significantly increased the levels of urinary Ca excretion whereas it suppressed the osteoblastic activity in the bone.

Acknowledgement: We thank Dr.Ayşe Yenigün, Dr.Çiğdem Yenisey, and Dr.İmran Kurt Ömürlü for their contributions.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:
Güngör SS, Sönmez F, Yılmaz D. The Effect of Corticosteroids on Urinary Calcium Excretion. A Pilot Study. J Clin Anal Med 2016;7(4): 524-8.